HERITABLE DISORDERS OF CONNECTIVE TISSUE

VII. The Hurler Syndrome

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HISTORICAL NOTE

THE disorder which is now called, among other names, the Hurler syndrome, is said by Henderson[48] to have been recognized by John Thomson of Edinburgh about 1900. The first definitive description was that of Charles H. Hunter* whose report appeared in the *Proceedings of the Royal Society of Medicine* in 1917 while he was serving in England as a major in the Canadian Army Medical Corps. This beautifully detailed and descriptive report concerned two brothers, aged 10 and 8 years, respectively, who were admitted to the Winnipeg General Hospital in 1915. The habitus was typically dwarfed. There were deafness, widely spaced teeth, short neck, protuberant abdomen with hepatosplenomegaly, inguinal hernias, short, broad, thick, stiff hands, semiflexed knees, noisy respiration. The elder boy had cardiomegaly and "a distinct diastolic murmur audible in the third and fourth left interspaces close to the sternum . . . ; at the apex, a systolic murmur was conducted towards the axilla." Twelve illustrations, including many x-rays demonstrating typical changes (such as "shoe-shaped" sella), were presented by Hunter. The boys appeared to be normally intelligent; clouding of the cornea was not observed; the spine was straight with loss of the normal contour but there was no gibbus.

In 1919 Gertrud Hurler of Munich[56] published cases at the suggestion of Professor Meinhard von Pfaundler,[88] who was chief of the University Clinic of Pediatrics and who had presented two patients with this syndrome to the Munich Society for Pediatrics on June 27 of the same year. The patients of Hurler and Pfaundler were infants; gibbus was present, as were corneal clouding and retardation of intellect.

It is surprising that Hunter's beautiful publication received, compared to Hurler's, relatively little attention. Subsequently, even in the English-speaking medical world, it was principally Hurler's paper which was referred to

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*Hunter was later Professor of Medicine in the University of Manitoba, Winnipeg. He died March 18, 1955, at the age of 82 years (Canad. M. A. J. 72:712, 1955).

and the names of Hurler and Pfaundler which became most firmly associated with the syndrome. (A similar situation exists in connection with the Morquio syndrome which was described in England by Brailsford slightly earlier than by Morquio of Montevideo.)

The nosography of the Hurler syndrome has now advanced to the point where the limits of the syndrome and its several clinical and pathologic features are reasonably well described, although mildly affected persons are still difficult to identify with certainty. A tabular survey of a large portion of the reported cases has been presented by Jervis.[63] Emanuel[36] estimated that over 200 cases had been reported by 1954.

Many different names have been suggested for this syndrome. Husler[57] suggested "dysostosis multiplex." Ellis and his co-workers,[34] Cockayne[17] and other English authors used the term gargoylism.* Washington[117] suggested lipochondrodystrophy, believing this to be a disorder of lipid metabolism. This is the term used by the *Cumulative Index Medicus*. However, it is probably a misnomer, as indicated by recent evidence bearing on the basic defect of the disease (see below). This is another instance demonstrating the desirability of using noncommittal terms in connection with these syndromes in which the basic defect is as yet unknown. Consistent with my practice with other syndromes discussed in this series, *the Hurler syndrome* is the designation which has been used here. Equally acceptable are the names of Pfaundler and of Hunter, which are sometimes associated with this condition.

In spite of Hunter's claim to priority, Hurler's name is selected for use because it is the eponym most firmly established in the literature. It is, after all, merely a symbol to indicate a clinical syndrome which is incompletely understood. Although there is some suggestion that what Hunter and Hurler described were genetically and clinically distinct entities (*v. seq.*), it is preferable to consider all these cases one syndrome, the Hurler syndrome, until the basic defect is more accurately known and methods for distinguishing precisely the possible subgroups of the syndrome are available.

Recently, Brante[11] has classified the Hurler syndrome as a mucopolysaccharidosis, and Uzman[113] has presented evidence that the defect is one of "structural polysaccharide." The development of views about the basic nature of this disease are discussed below in the section dealing with that particular aspect.

CLINICAL MANIFESTATIONS

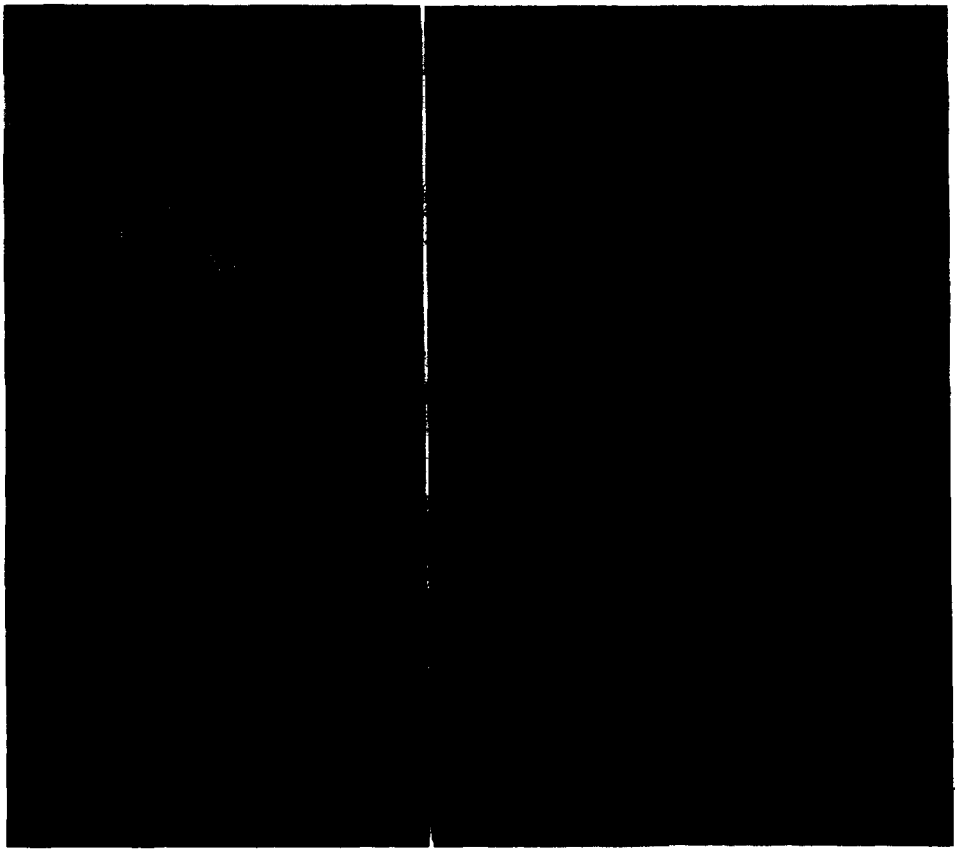
The clinical description provided here is based on the findings in sixteen patients with the Hurler syndrome seen at this hospital and at the Rosewood State Training School.

The cardinal features of this syndrome are disproportionate dwarfism with a characteristic, grotesque skeletal deformity, limitation of joint motion, deafness, hepatosplenomegaly, cardiac abnormality (either from the outset or developing

*This seems an unnecessarily cruel term in view of the fact that the intellect may be little impaired and survival to adulthood is not infrequent. It is scarcely a diagnosis which can be cited to a parent, for example. Families sometimes raised legitimate objections to such statements (all too frequent in the literature) as these: "He is a typical gargoyle"; "there are three gargoyles in this family."

with the passage of years), clouding of the cornea, and mental retardation. The last two features need not be present.

The patient frequently appears normal at birth but, with the passage of the first year (a "symptom-free interval"), becomes manifestly abnormal. The lines along which development occurs in these patients is so similar from patient to patient that, as in the Marfan syndrome, myotonic dystrophy, Mongolism, and other conditions, the patients, even though unrelated, tend to resemble each other more than their unaffected siblings.



A. *B.*

Fig. 1.—Thirty-four-month-old child (S. S., B3747). The child is mentally retarded. The liver and spleen are enlarged, the corneas cloudy, and the teeth short, abnormally formed and late in appearing. The fingers show flexion contractures as do other joints to a slight extent. There is constant nasal congestion so that the patient is a mouth-breather. Most of these features are evident in *A*. In *B* the lower dorsal, upper lumbar gibbus is evident. The skeletal basis for this appearance is shown by the x-ray of the spine in *C*. Note the lumbar kyphos, beaking of the lumbar vertebrae, the sabre-shaped ribs, hepatosplenomegaly.

The head is large and bulging, often with prominent scalp veins in the case of small children. The bridge of the nose is flattened, creating a saddle appearance. Hypertelorism is usual. The skull is often scaphocephalic,* i.e., shaped like the keel of a boat, seemingly as a result of premature closure of the sagittal and metopic sutures with hyperostosis in those areas. This hyper-

*There is usually no difficulty in distinguishing the Hurler syndrome from the specific conditions given the generic names *acrocephaly* and *scaphocephaly*,[87] although in the earlier days of the nosography of Hurler's syndrome such confusion did occur.[64]

ostosis often creates a longitudinal (sagittal) ridge which may cross the forehead. Radiologic changes in the sella turcica in the form of unusual length and shallowness and an anterior "pocketing" (Figs. 2,*C* and 3,*C*) are striking and virtually pathognomonic. This type of sella is called "shoe-shaped" by Ullrich,[111] who found in other cases a shallow "shell-shaped" or a deeper "bowl-shaped" fossa.

The lips are large and patulous. These, with the apathetic facies, the open mouth, and frequently enlarged tongue, may lead to a false diagnosis of cretinism. In general, the facial features are coarse and ugly. The teeth are usually small, stubby, widely spaced, and malformed. In many of the cases there is hypertrophy both of the bony alveolar ridges and of the overlying gums.[22] Chronic "rhinitis" with noisy mouth breathing is virtually universal in this group of

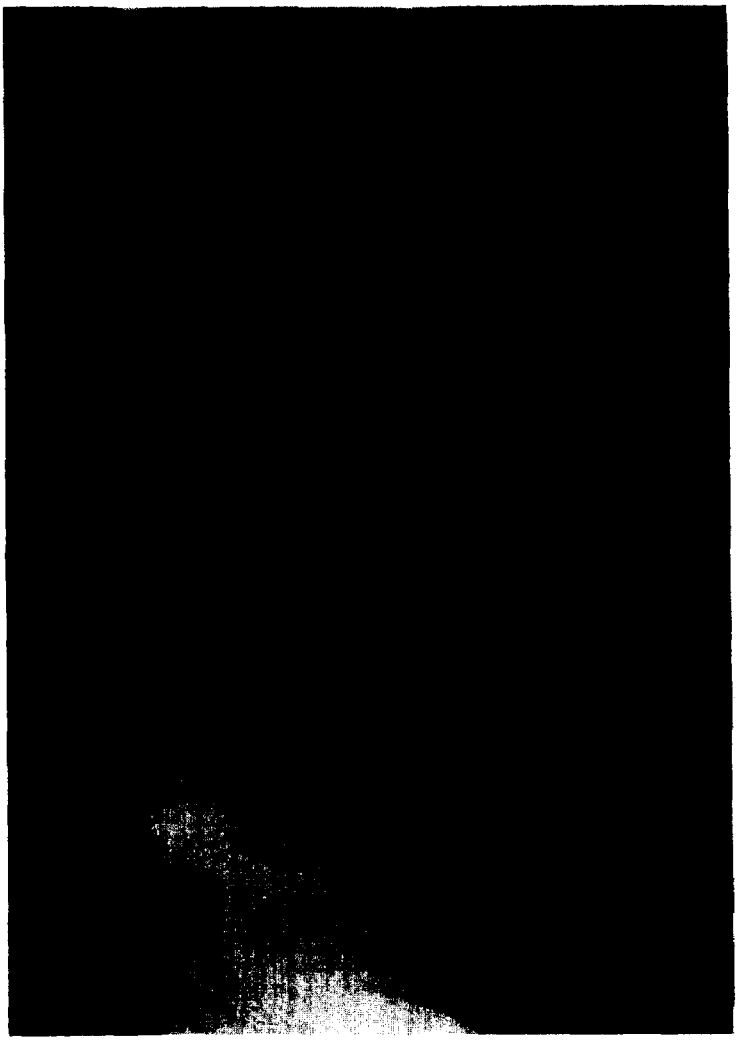
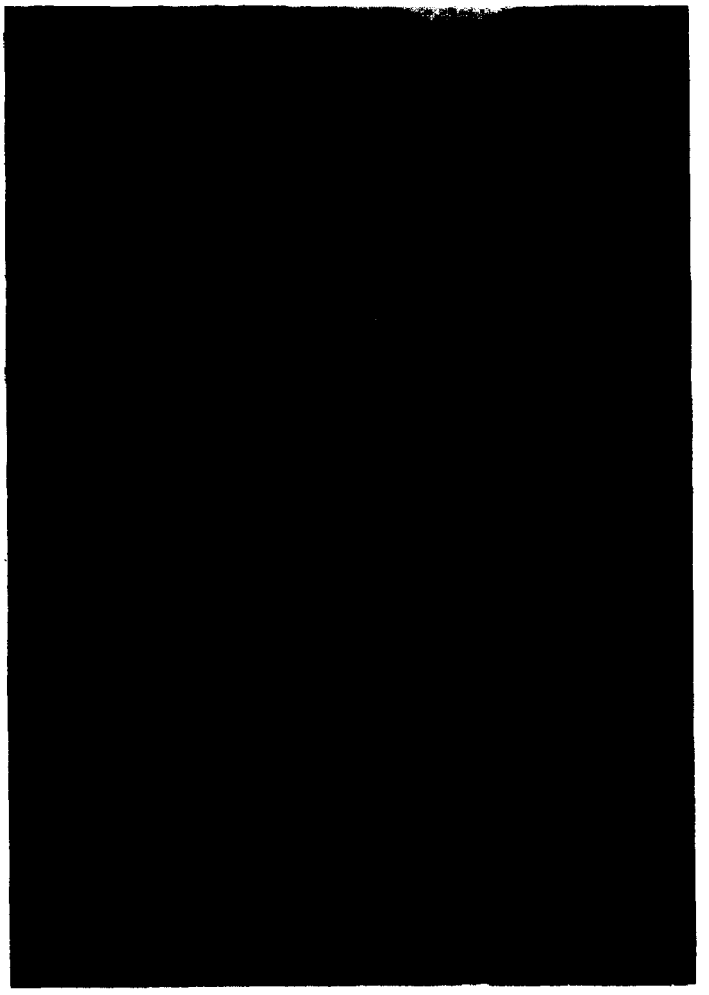


Fig. 1,*C*. *(For legend see opposite page.)*

patients. X-rays of the facial bones usually show marked deformities which are probably responsible for the nasal manifestations. On lateral view of the skull, it can often be seen that a mass of adenoid tissue in the nasopharynx is narrowing or obliterating the normal air shadow.

The neck is exceedingly short, and the thorax, on which the head appears to rest directly, is deformed. There is usually a flaring of the lower rib cage, prob-

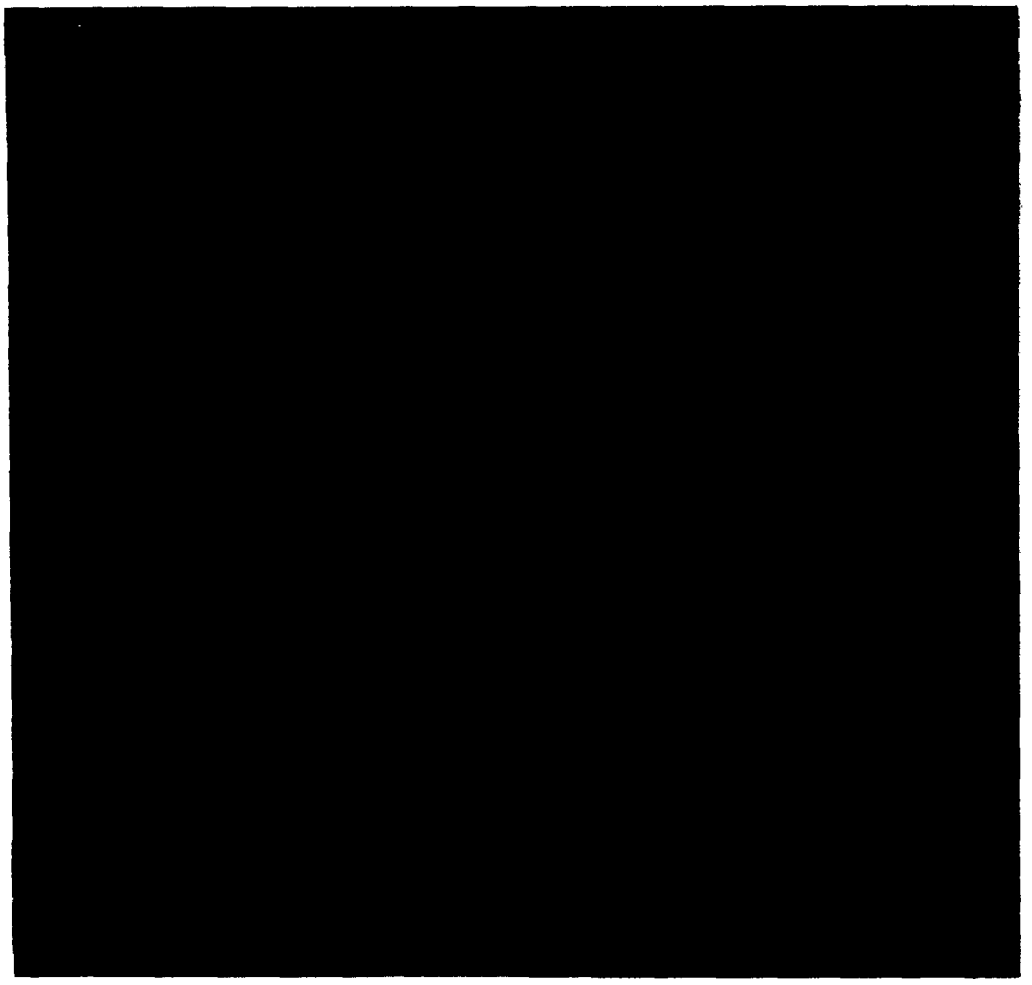
ably due in part to the hepatosplenomegaly. Kyphosis with gibbus in the lower thoracic and upper lumbar area is likely to be present. Myelograms in one case revealed partial obstruction of the spinal canal at the level of the gibbus. Radiologic examination usually shows a wedge-shaped deformity of the body of the vertebrae with an anterior hooklike projection, so-called beaking of the vertebrae.



A.

Fig. 2.—Skeletal changes in the Hurler syndrome. *A*, The lower ribs are unusually broad and spatulous. Note the evidence of hepatosplenomegaly. *B*, The anterior pocketing of the sella, "shoe-shaped" sella, is highly characteristic. Furthermore, pronounced abnormality in the region of the paranasal sinuses is evident. *C*, The long bones of the arm are abnormally short and broad. The bones of the hand are strikingly abnormal in configuration. Again their shape is virtually pathognomonic of the Hurler syndrome.

The hands are usually broad with stubby fingers.[102] The fifth fingers are often bent radially, and, in general, there is likely to be at least partial flexion contracture of the fingers as well as of the larger joints. Limitation in extensibility of joints is usually striking.[56] This feature may be due both to deformity of the joint surfaces and to changes in the tendons and ligaments surrounding



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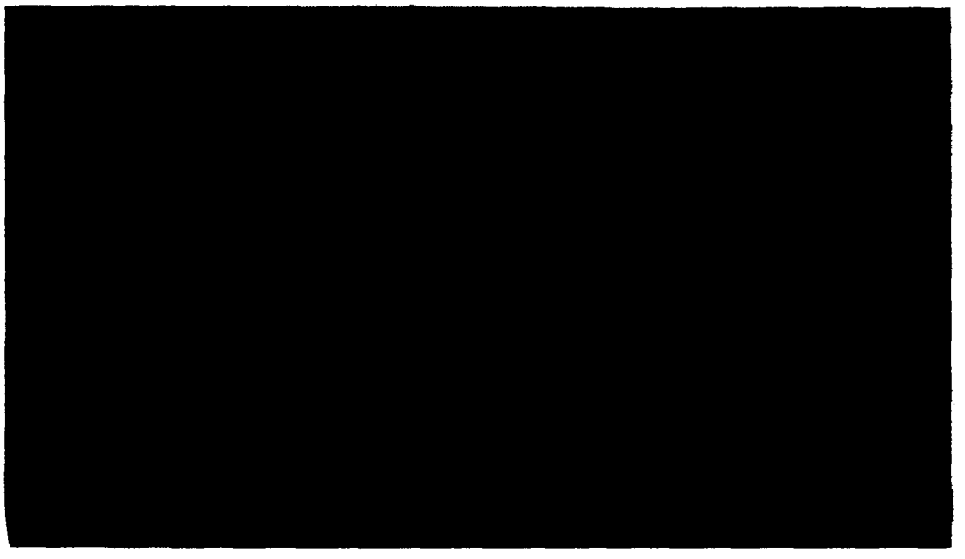
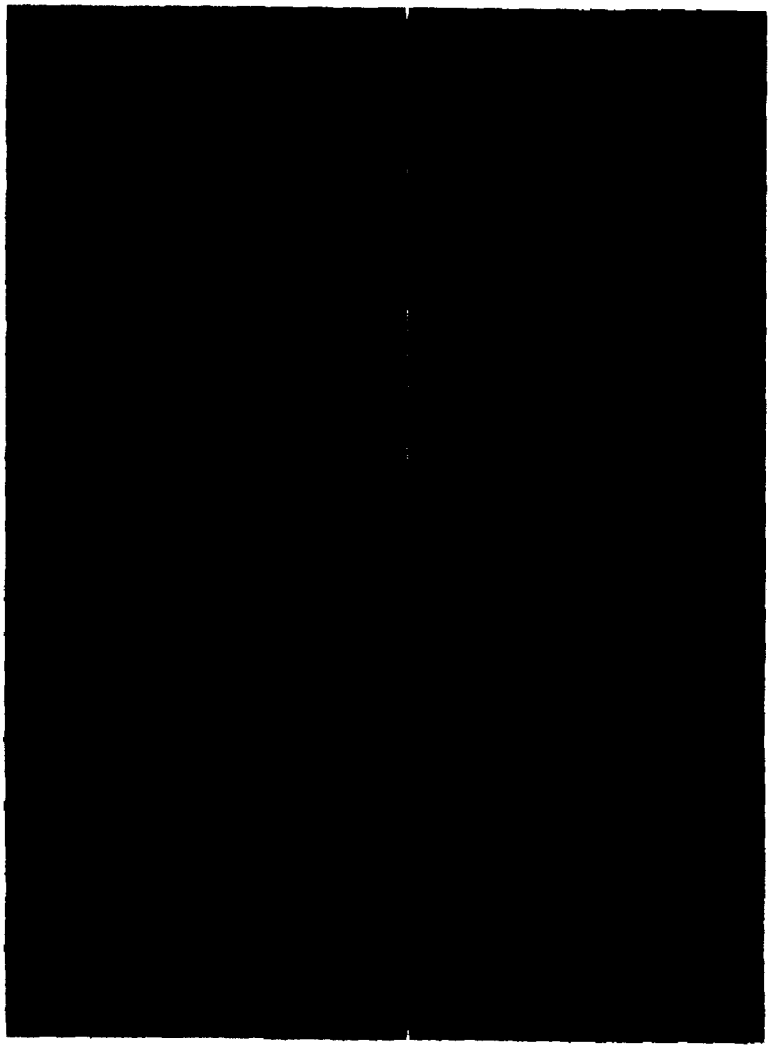


C.

Fig. 2, *B* and *C*. (*For legend see opposite page.*)

the joints. As a result, the patients often find it necessary to walk on their toes, especially if they have been in bed a good deal. A deformity of the wrist may superficially suggest rickets. However, the stiff joints (along with many other features) help distinguish the Hurler syndrome[52]; the joints in rickets are more limber than normal. The limitation of motion of joints seems to extend to the thorax, which often is relatively fixed in position.[36]



A.

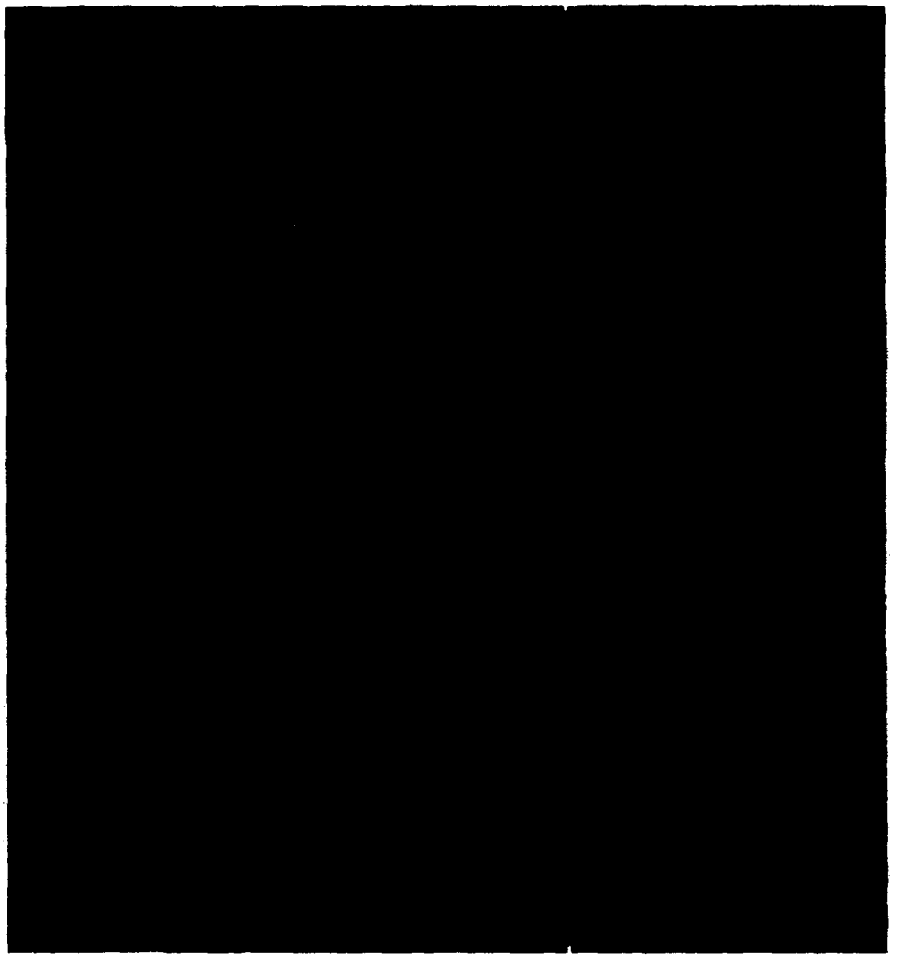
Fig. 3.—Typical case of the Hurler syndrome (I. S. 204375). *A*, At the age of 10 years.

The gibbus is often the first observed abnormality. When the infant begins to sit, he is likely to assume a posture like a cat's in sitting (Fig. 1,*B*), the "cat back deformity."

In addition to the radiologic changes already described in the skull and in the vertebral column, the bones of the extremities are abnormal in appearance. The phalangeal bones, for example, are short and misshapened (Fig. 2,*D*). The ribs are characteristically broad, sabre-shaped, or spatulate (Figs. 2,*A*, 2,*B*).

Genu valgum, coxa valga, pes planus, talipes equinovarus, and other deformities occur frequently. Hooper's patient[51] was operated upon for talipes equinovarus at the age of 17 years. Spina bifida occulta is occasionally present.

The abdomen is protuberant, due in part to hepatosplenemegaly, in part to the defect of the supporting tissues. Both liver and spleen may be so large that their lower borders dip into the pelvis. One patient developed pancytopenia and epistaxes, possibly on the basis of hypersplenism.[102] Lindsay[71] described an abnormal hippuric acid test in one patient, and, in another, prolonged elevation of galactose in the blood after intravenous injection. The number of patients



B. *C.*

Fig. 3.*B* and *C*.—Same patient at the age of 22 years.

tested was not stated. Although no systematic study has been made, the impression is given that surprisingly little functional impairment results from the marked gross and histologic involvement of the liver. One case of cirrhosis of the liver in a 37-year-old patient with quite typical Hurler's syndrome has been reported by Schwarz and Gagne.[98] Portal hypertension, massive ascites, hematemeses, melena, and death resulted. At necropsy the liver was found to weigh only 900 grams. In a 29-year-old patient[102] with fairly marked hepatospleno-

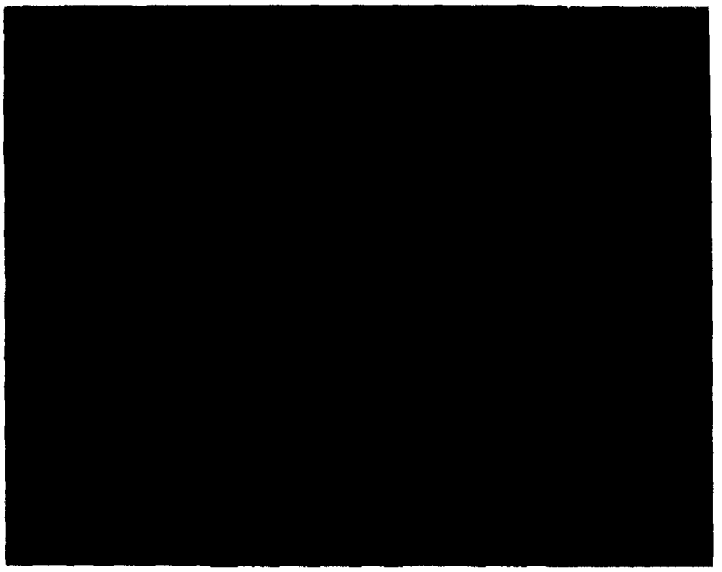


Fig. 3,*D*.—The hands.

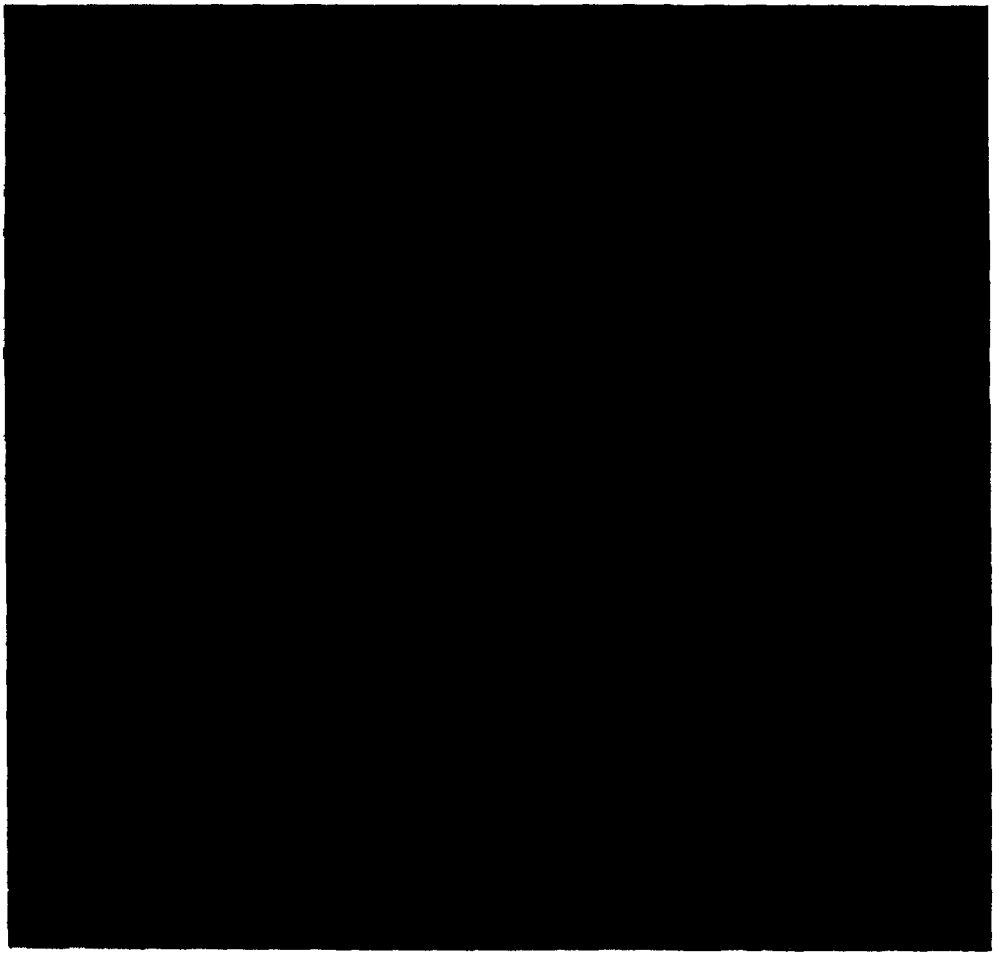


Fig. 3,*E*.—Lateral radiograph of skull. Characteristic anterior pocketing of the sella is present. There are obvious frontal and occipital areas of hyperostosis. The mastoid air-cells are underdeveloped and in general the mastoid is more dense than normal.

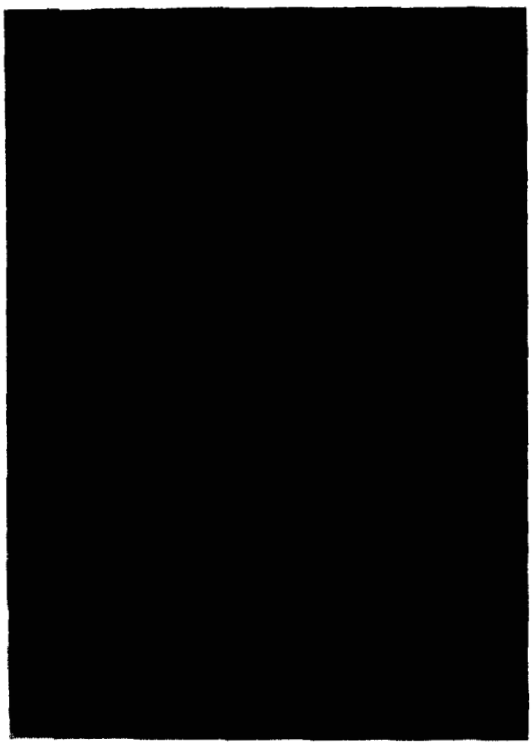


Fig. 3,*F*.—Two uncles of the patient. Both probably had the Hurler syndrome.

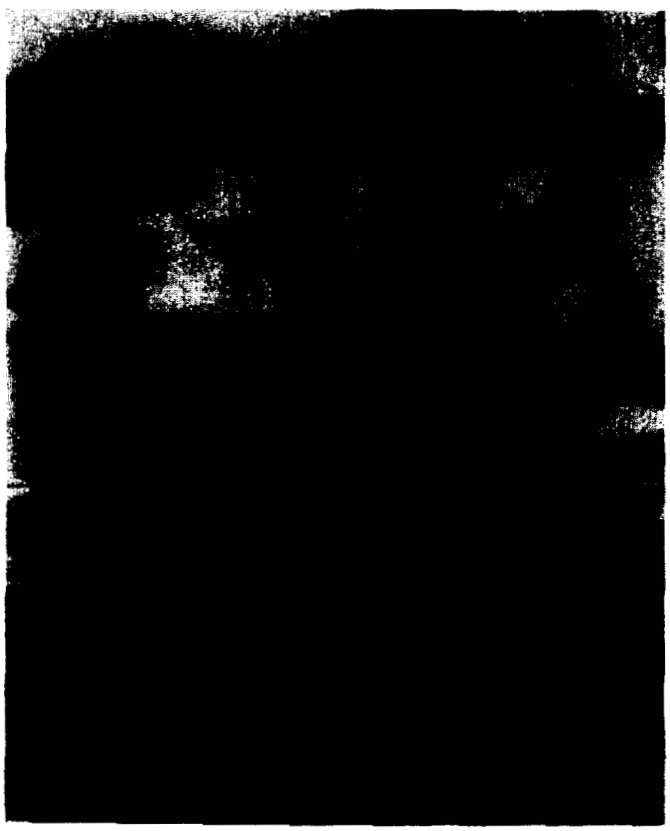


Fig. 3,*G*.—The propositus (on left), aged 22 years, and his unaffected brother (on right), aged 8 years.

megaly, cephalin flocculation, thymol turbidity, total serum proteins, albumin-globulin ratio, prothrombin time and bromsulfalein excretion were all unequivocally normal. Many of the patients in my series have had these same tests with similarly normal findings. Moderate increases in serum cholesterol concentration do seem to occur more often than is normal and may be related to the liver disease.

Diastasis recti and umbilical hernia are almost invariable and inguinal hernia in frequent. Engel[37] described scrotal hernias the size of a child's head. Bilateral hydrocele is also seen.[47]

"Funnel chest" was present in one of Hurler's cases[63] and one of mine.

Changes in the skin[69] in the form of grooving and either ridged[19] or nodular[1] thickening, expecially over the upper arms and thorax, have been described. In two of the reports[1,19] the changes were strikingly similar, especially as to location —"symmetrically distributed in an area of about 6 by 10 cm., extending from the angle of the scapula towards the axillary line." In most of the cases the entire surface of the body, both trunk and extremities, is covered by fine, lanugo-like fuzz. In older patients, too, hairiness is quite striking, especially over the arms and hands (Fig. 3).

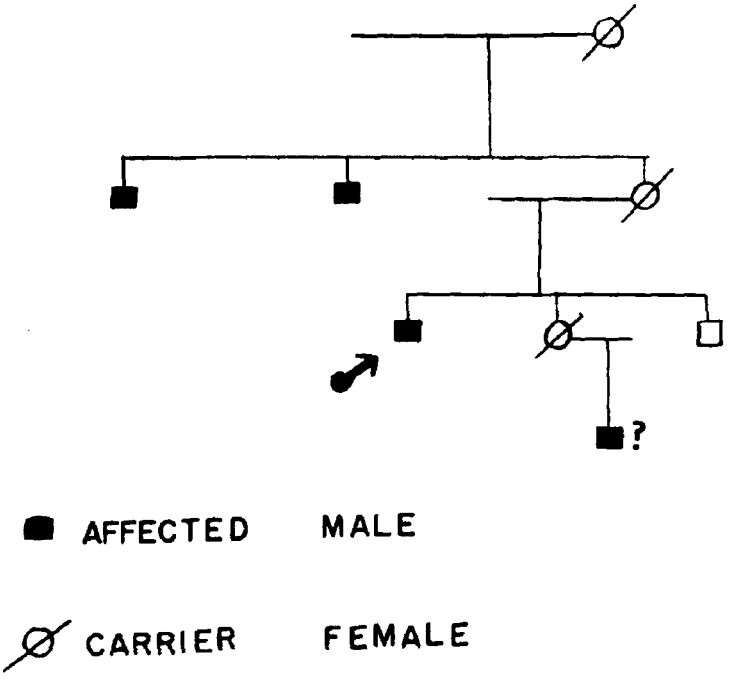


Fig. 3,*II*.—Pedigree. The propositus is indicated by the arrow. The probable occurrence in four males in three generations is consistent with, and at least mildly indicative of, inheritance of the trait as a sex-linked recessive. The females marked with the line, in fact all the females included in the pedigree, are presumed to be genetic carriers for this trait.

This patient, 22 years old in Fig. 3,*B* and on most recent study, has dysostosis multiplex, deafness, "chronic rhinitis," exertional dyspnea, hepatomegaly, restricted joint mobility, hydrocele, and hernia, but no splenomegaly or corneal opacification. Mentality is retarded. The patient graduated from high school because of courtesy promotions. He reads voluminously, especially Ellery Queen novels! No inclusions could be demonstrated in the white cells. The testes are small and soft. However, the patient shaves daily and erections and nocturnal emissions occur. Vision was 20/100 in the right eye, 20/30 in the left. A startling finding was bilateral papilledema, probably long-standing, with "bone corpuscle" pigmentary degeneration of both fundi, especially the right. A peculiar feature has been the subjective response to thyroid. Two maternal uncles (Fig. 3,*E*) had the Hurler syndrome with characteristic skeletal features, deafness, and symptoms of cardiac incompetence. They died at the ages of 12 and 17 years, one having been found dead in bed. The patient's parents are normal and he has two normal siblings. An 8-month-old nephew of the patient may have the disease; I have not had an opportunity to examine the child but the descriptions are suggestive.

No consistent endocrine abnormality is clinically detectable, in spite of the histologic evidence of cellular deposits in most glands of internal secretion. Thyroid enlargement without dysfunction has been described and is probably related to the histologic infiltration referred to. Hypoglycemia from hepatic involvement is thought to be a risk but has not actually been demonstrated to my knowledge.

Inclusions (Adler bodies) in the polymorphonuclear leukocytes are sometimes found.[90] These are described as being larger than the ordinary granules and tending to take a dark lilac color when stained by the Giemsa-Wright technique. In a number of the cases seen in this hospital, Dr. C. L. Conley has looked for inclusions without success. Although others[9,31] have confirmed Reilly's[90] original observation, the occurrence of leukocytic granules may not be as frequent as often thought.[113] The inclusions have histochemical characteristics suggesting identity with the material which balloons cells of other parts of the body.[72] (Apparently, inclusions may also occur in the leukocytes in glycogen storage disease.[12,116])

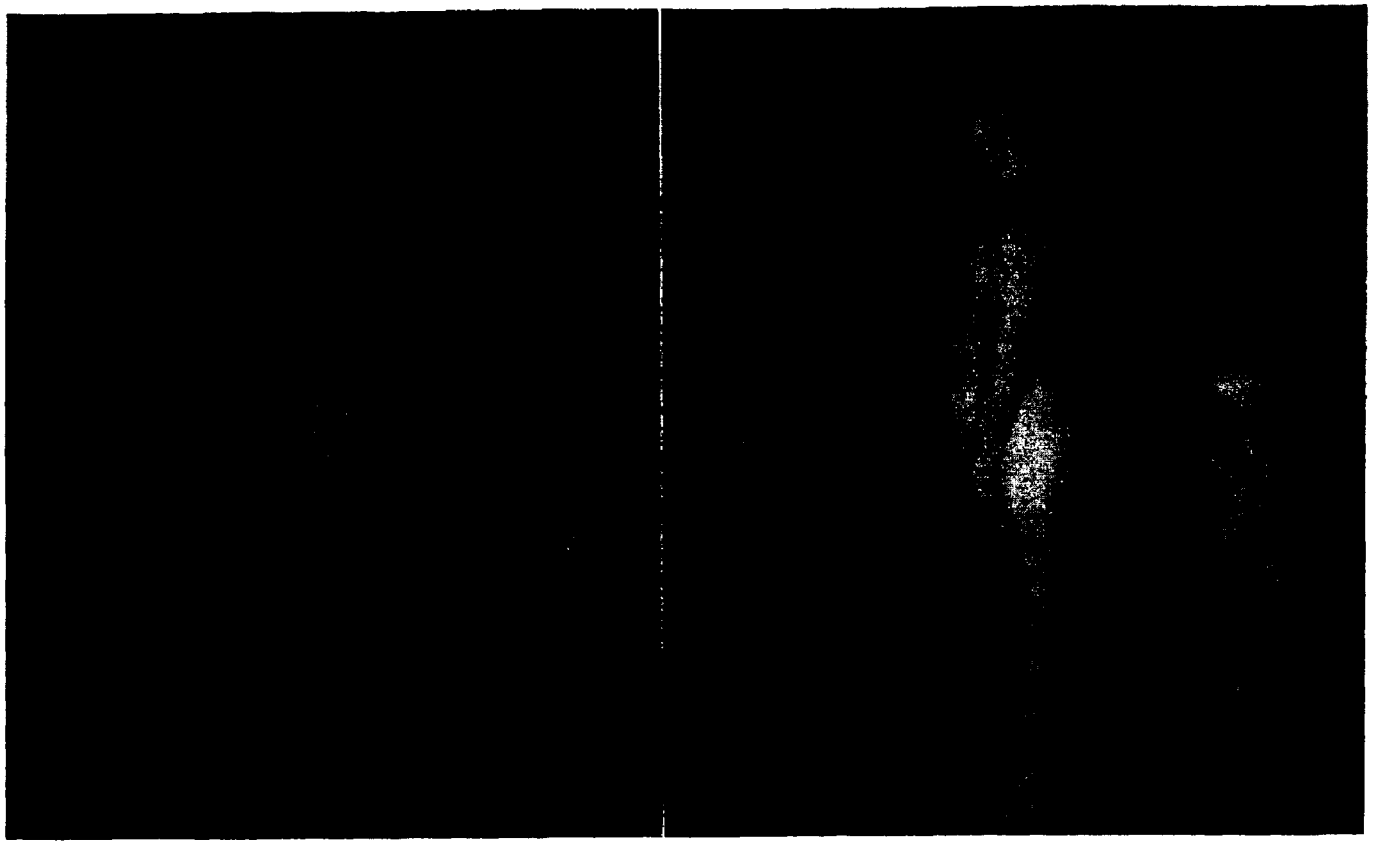
Clouding of the cornea has been described in about 70 per cent of reported cases. The cornea usually has merely a steamy appearance in earlier stages. On inspection this feature is most apparent if light is shined on the cornea from the side.

Ullrich[111] found, up to 1943, fifty-one cases with corneal involvement, eighteen without. Although the number of cases with evidences of corneal involvement is increased by slit-lamp examination, there are certainly some with none. Slit-lamp reveals that the opacities are located in the medial and deeper layers of the cornea. The epithelium and endothelium are spared. Other ocular abnormalities such as buphthalmos[26] and megalocornea[5,34,63,80] have been described. There may be a retinal element in visual impairment since histopathologic changes in the retina have been described.[72] The occurrence of papilledema in these patients (see Fig. 3) has suggested hydrocephalus, or at least increased intracranial pressure. Optic atrophy was described in two siblings by Davis and Currier.[26]

Mental retardation may be only mild in some cases. Hydrocephalus may occur in severely affected infants.[2,71] Some cases may show simple dilatation of the ventricles secondary to cortical atrophy.[111] The mental deterioration is likely to be progressive, resembling juvenile amaurotic idiocy in this respect.[63] There may be accompanying neurologic signs such as motor paralysis, increase in muscular tone, and the Babinski sign.

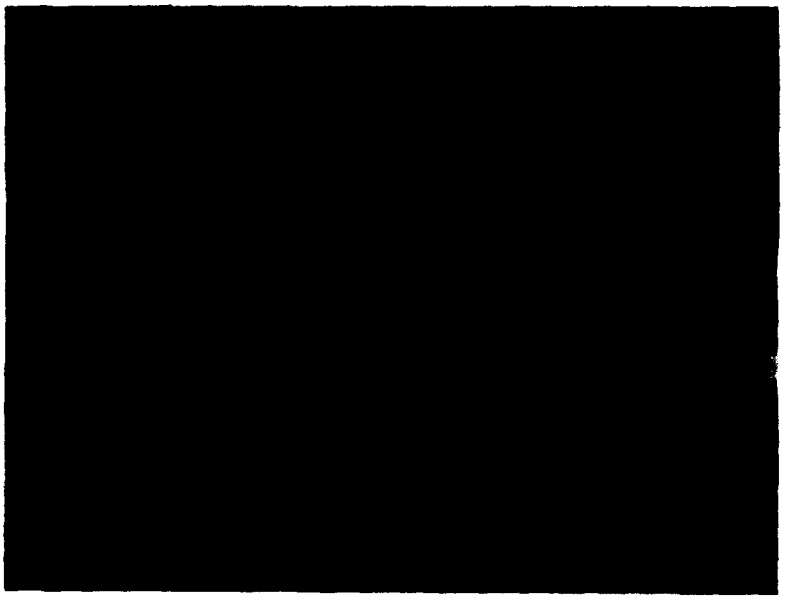
One would presume that the deafness is in the main secondary to the bone disease as in osteogenesis imperfecta. In a 24-year-old patient studied by Dr. William G. Hardy of the Johns Hopkins Hearing and Speech Clinic, the deafness was found to be of perceptive type. In a 16-month-old child it was of the conductive type, and in a 3-year-old patient hearing was unimpaired. Because of the deformity of the nasopharynx, these patients probably have more than the average susceptibility to middle-ear infection. Furthermore, the ossicles have shown deformity with limitation of joint motion as in other joints and bones.[120] Therefore, a conductive element in the deafness of some patients is to be expected.

Nasal congestion, noisy mouth breathing, and frequent upper respiratory infections occur in essentially all patients with the Hurler syndrome. The malformation of the facial and nasal bones is probably in large part responsible.



A. *B.*

Fig. 4, *A* and *B*.—Three siblings, aged 8, 6, and 12 years, respectively, left to right. The brother in the middle, aged 6, is normal. The brother and sister on the sides have been thought to have Morquio's syndrome, but review of the total clinical picture suggests that Hurler's syndrome may be present. They are markedly dwarfed. There is limitation of motion of many of their joints. This is visible in the pictures. Contractures of the fingers began to develop at the age of about 18 months. The immobility of joints is in part the result of distortion and dislocation of the epiphysis but seems in part the result of changes in connective tissues about the joints. There is no gibbus, but by x-ray beaking of lumbar vertebrae is demonstrated (Fig. 4,*E*). Mentality is roughly normal and both children are lively and energetic. Teeth are wide-set, piglike, susceptible to caries. Both children are already somewhat deaf. The 8-year-old affected brother has hypospadias; sexually the affected sister appears to be developing normally although catamenia has not yet occurred. The affected boy had a strangulated left inguinal hernia at the age of 1 year, and a strangulated right inguinal hernia at the age of 2 years. Umbilical hernia has been present for several years. Both children have heart murmurs. The boy's is apical, the girl's basilar. In both, the murmur has a groaning quality and is believed to be innocent. The parents are normal and there are two other normal children. In the affected girl the liver and spleen are not thought to be enlarged. In the boy the liver was 4 to 6 cm. below the costal margin and the spleen was 4 to 5 cm. down (at the age of 3 years neither had been considered enlarged). In both, the corneas are clear. ECG and EEG are normal. It is not difficult to understand why the idea has arisen that the Morquio syndrome may occur in one member of a sibship and the Hurler syndrome in another.[8]



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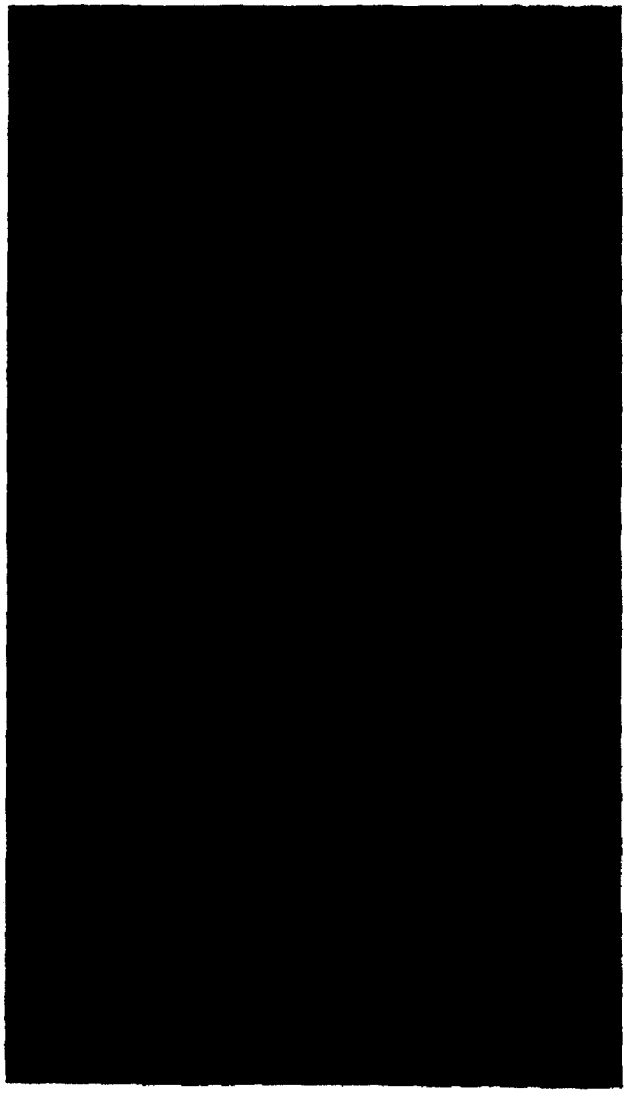

C.

Fig. 4.*C.*—The fingers are being held in maximum extension possible. Note the contractures.

Fig. 4 *D.*—X-ray of the hands revealed moderate coarsening of the bones but not as marked changes or the specific change in shape seen in Fig. 2,*D*. The contractures seem to be the result of changes in the soft tissues.

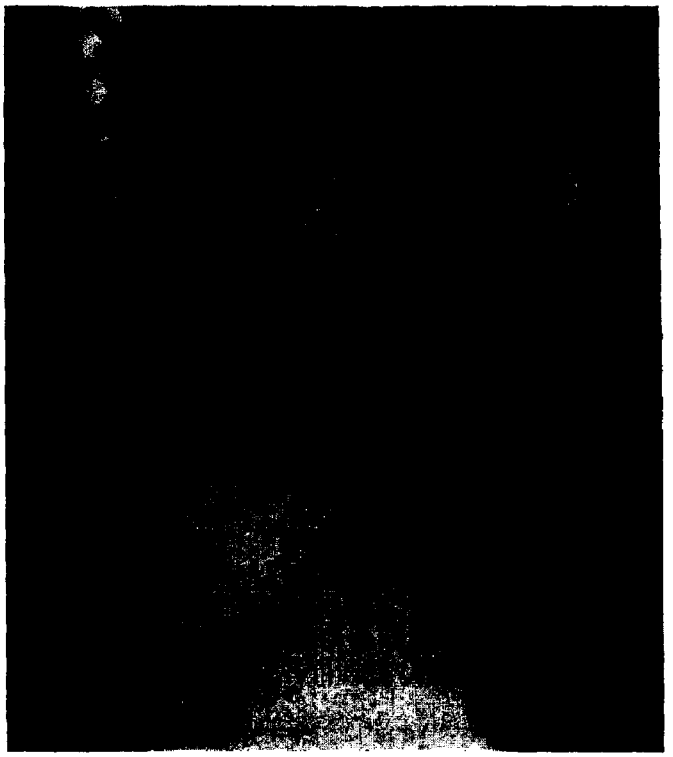

Fig. 4,*E*.—Lateral view of the spine in affected girl. Note the same sabrelike ribs and beaking of the lower margin of the vertebrae as in Fig. 2,*B*.

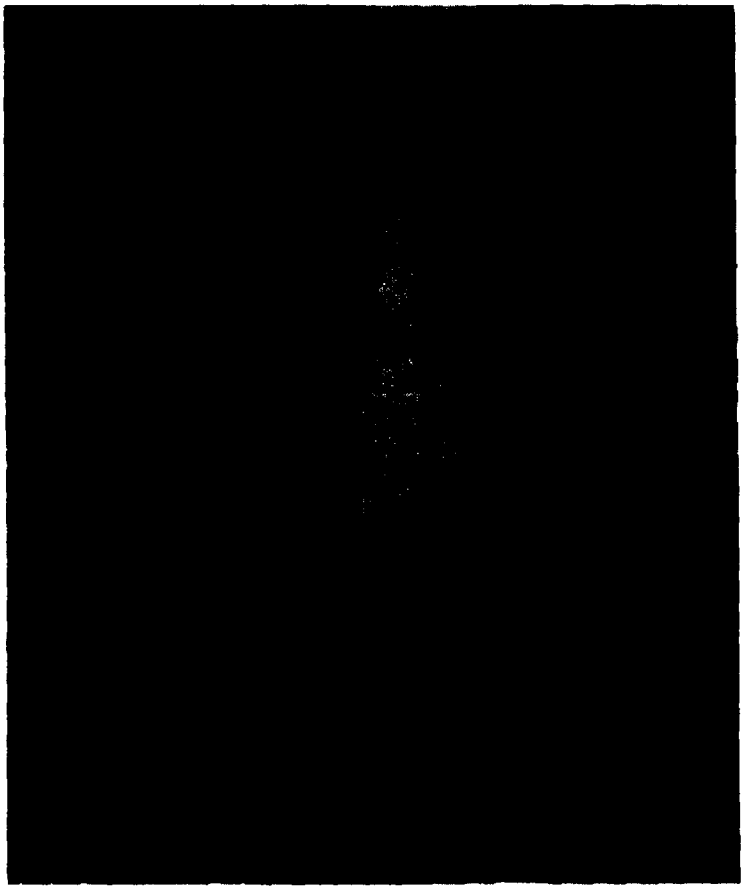

Fig. 4,*F*.—Frontal view of skeletal system in affected girl. Note the advanced changes in the epiphyses of each femur and humerus.

Ellis, Sheldon, and Capon[34] commented on this feature. Most other writers have also emphasized it and considered malformation of the nasopharynx to be its basis.

In Hunter's historic report[55] he remarked on the occurrence in one of his patients of cardiomegaly and both systolic and diastolic murmurs. Murmurs were described also by Meyer and Okner,[80] Engel,[37] and others. Ashby, Stewart, and Watkins[2] described "congenital heart disease" as the cause of death at 9 years of

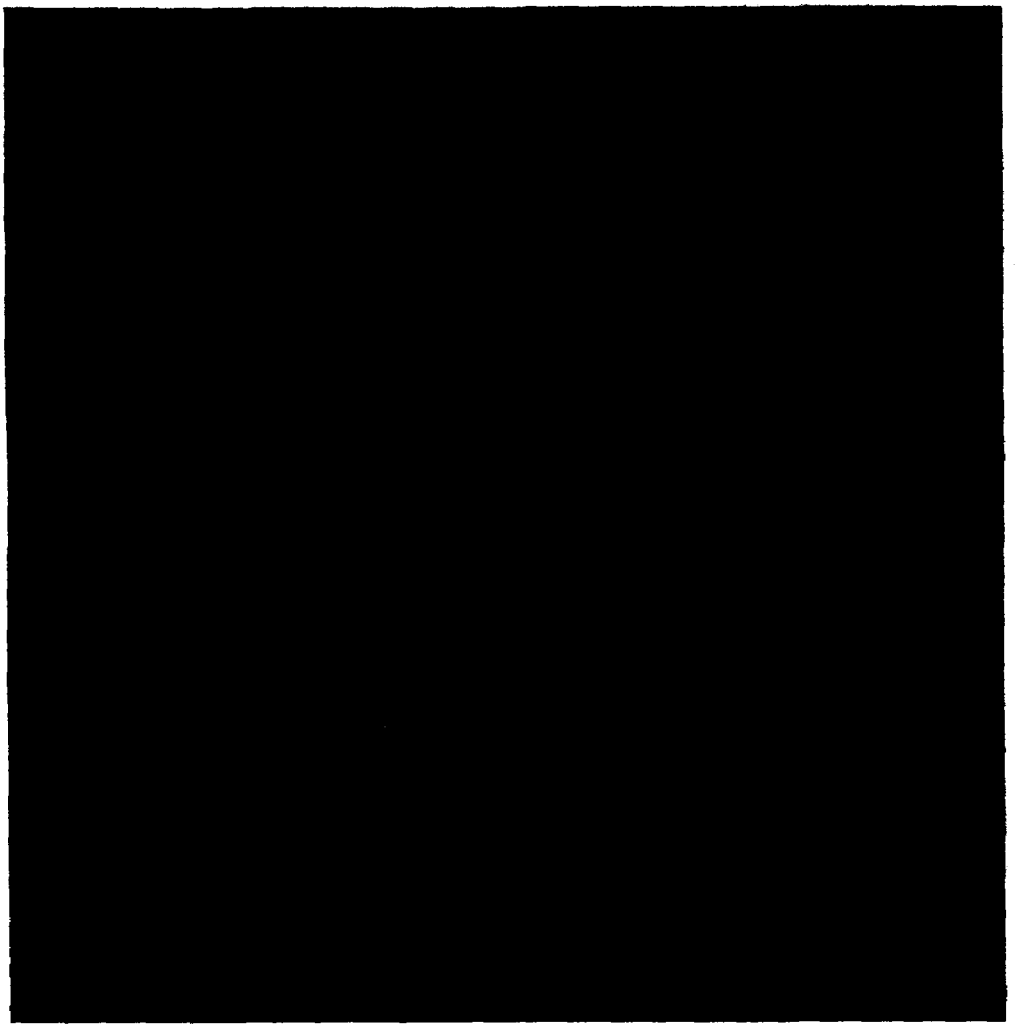

Fig. 4,*G*.—Note marked anterior pocketing of the sella. Compare with Fig. 3,*C*. Clinically there is a ridge running sagittally over the skull (scaphocephaly).

age in one child and in a 19-year-old patient who died suddenly. Mouth breathing and dyspnea from thoracic deformity and restriction of expansion[36] (which may be very striking), abnormality of the bronchial cartilages, and, finally, frequent attacks of bronchitis make it difficult to dissect out that part of the dyspnea which is on a cardiac basis. The best specific descriptions of the cardiovascular aspects of the Hurler syndrome are those of Lindsay[71] and Emanuel.[36] Emanuel described in two brothers cardiac signs he interpreted as being those of pulmonary hypertension. In one, cardiac catheterization was performed with demonstration

of a much elevated pulmonary artery pressure (88/50 mm. Hg). The peripheral arteries of the arms were described as thickened in a 6½-year-old child[72] and there was hypertension (132/100 mm. Hg).

What was interpreted as angina pectoris occurred[22] as early as 4¾ years of age in a child who died at the age of 7 years. The extensive occlusive disease of the coronary arteries discovered at autopsy in this child would suggest that this is the basis of sudden death in many of these patients.

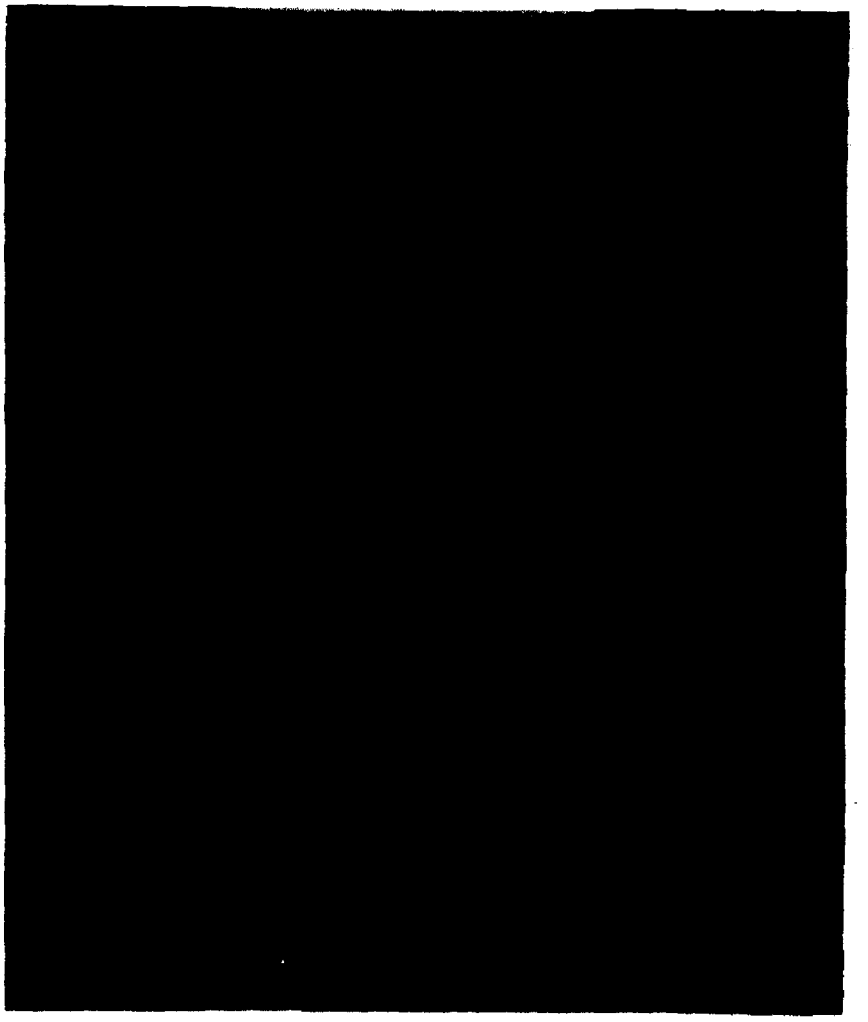

Fig. 5.—Chest x-ray in G. V. D., Jr. (B2188), aged 4½ years. This patient has the Hurler syndrome in entirely typical form. He reached a peak of intellectual development at about 2 years and has deteriorated since then. Gibbus was noted at 1 year. Thick skin, lanugo, "shoe-shaped" sella, and ground-glass corneas are present. Hydrocele and right inguinal hernia were treated surgically at the age of 1½ years.

The central infiltration of the lung fields was present in an unchanged form for at least six months. Tuberculin skin tests are negative. The changes are believed to be the result of chronic bronchitis. However, interstitial pulmonary infiltration as part of the disease and analogous to the infiltrations elsewhere cannot be excluded.

Lindsay[71] stated that systolic murmurs along the left sternal border were so striking in these patients that four of sixteen were suspected of having an

interventricular septal defect. There was a similar clinical experience in the group of cases at this hospital. The experience with other heritable disorders of connective tissue, specifically the Marfan and Ehlers-Danlos syndromes, in which cardiac malformations of the conventional type occur with predictably increased frequency, suggests that the same might occur in the Hurler syndrome. Pathologic studies have not corroborated this suspicion (see below). Although some cardiovascular abnormality was present in the great majority of patients who have died, all the changes have been of a specific type, as described later.

Death from "heart failure" (either congestive or coronary artery in type) often occurs before the age of 20 years. Of the patients described by Smith, Hempelmann, Moore, and Barr,[102] one died at the age of 28 years and another was "reasonably well" at 29 years of age. Hooper[51] described a 37-year-old patient who was still living. In two of his other patients, death occurred at 20 and 30 years of age, respectively. The two oldest patients in my series are 22 and 25 years old, respectively (see Fig. 3 for one of these). Beebe and Formel[4] described nine well-documented cases of the Hurler syndrome in one family. Five had died at an age in excess of 40 years. There were four survivors aged 45, 43, 17, and 14 years, respectively.

PATHOLOGIC CHANGES[38]

At least thirty autopsies have been reported in detail: eighteen individual reports,[2,4,30,36,42,49,66,67,68,76,81,96,98,102,105,106,110,111,113,117] two by Jervis,[62] and eight by Lindsay, Reilly, Gotham, and Skahen.[72] Jackson[58] and others have reported on biopsies of the liver.

Among other sites, abnormalities have been identified in cartilage, fasciae, tendons, periosteum, blood vessels, heart valves, meninges, and cornea. All of these may contain cells which are thought to be of the fibroblast line and which are distended with large amounts of deposited material. These are appropriately called "clear cells" by Millman and Whittick,[81] but perhaps it would be preferable to use the more specific designation "gargoyle cells."[109] In addition, collagen in many of these areas has been said to look abnormal in a poorly defined way. Collagen fibers are described by some (e.g., ref. 71) as swollen, homogeneous, and lacking in their normal fibrillary characteristics. Material, presumably identical to that in the fibroblasts, balloons the nerve cells of both the central nervous system and the peripheral ganglia, the nerve cells in the nuclear layer of the retina,[72] the Kupffer cells of the liver, the parenchymal cells of the liver, the reticulum cells of the spleen and lymph nodes, and the epithelial cells of several endocrine organs such as the pituitary[68] and testis. Mental retardation and hepatosplenomegaly are explained by these deposits.

Enlargement and vacuolization of the chondrocytes and osteocytes, as well as of the periosteal cells, are described and probably are intimately related to the skeletal malformation.

In the heart, in persons dying after a few years of life, the aortic and mitral valves almost invariably have shown some degree of nodular thickening.[36,72] Functionally both stenosis and regurgitation can result. In the case of Smith and co-workers[102] the histologic picture in the heart valves was dominated by the

presence of "gargoyle cells." These have also been seen in the coronary arteries.[72,76] Grossly[36] even in young individuals the coronary arteries may "stand out like white cords." Virtually complete occlusion may result from the extensive intimal deposits.[22,27] The aorta[76] and pulmonary artery[36] may show extensive intimal deposits, presumably of the same material as forms the vacuoles of the cells of various organs. The myocardial cells may show marked ballooning by vacuoles (see photomicrograph, ref. 6). Patchy thickening of the endocardium and epicardium is described.[36,72,106] Of the peripheral arteries, changes have been described in those of the brain, spleen, pancreas, and kidney as well as in the mesenteric, carotid, radial, and anterior tibial arteries.

Emanuel[36] was able to find 32 autopsy reports in which specific description of the heart was provided in 26. Of these 22 had cardiovascular abnormalities (85 per cent). In 15 patients the mitral valve was deformed, in 9 the aortic, in 7 the tricuspid, and in 2 the pulmonary. In three (including Emanuel's case) all four valves, the epicardium, the endocardium, the coronary arteries, and the aorta and pulmonary artery were involved.[72,106]

It is of note that the order of incidence of involvement of the heart valve—mitral, aortic, tricuspid, pulmonary—is precisely as in rheumatic fever. In both situations there are probably operating at least two prominent factors. The metabolic aberration (in one case acquired, in the other inherited) and the hemodynamic stresses. The peak pressures sustained by the four valves in the position of closure are in the same sequence as the incidence of valve involvement: mitral, 120* mm. Hg; aortic, 80 mm. Hg; tricuspid, 25 mm. Hg; pulmonary, 12 mm. Hg.

A conventional type of congenital malformation of the heart has been thought clinically to be present in three of the patients seen at this hospital. Seemingly, however, no such malformation has been revealed by any of the pathologic studies.

Abnormality of the tracheobronchial cartilages together with that of the upper airways may be responsible for the susceptibility to respiratory infections in these patients. Bronchopneumonia is a frequent cause of death.[63]

Cole and associates[19] illustrate a histologic section of skin which was interpreted as showing "marked fragmentation of collagen fibers and mucinous degeneration."

Vacuolated cells have been described in Bowman's membrane by Berliner[6] and others. Lindsay and co-workers[72] described highly metachromatic granules in the cornea.

Multiple abnormalities in the middle and inner ear have been discovered in one twice-reported case.[102,120]

Extensive changes in the leptomeninges were described by Magee.[76] The coincidence of subdural hematoma in his case makes these changes difficult to interpret. Millman and Whittick[81] found thickening of the leptomeninges over the cerebral hemispheres and "clear cells" histologically. In Njås[85] case 2, there was hydrocephalus with "thickened and milky leptomeninges." The hydrocephalus may be the result of interference with drainage produced by the deposits characteristic of the disease.

*All values are approximations.

Some have reported that the intracellular deposits do take the conventional fat stains.[6,46,110] Most have found that the vacuoles do not stain as fat or stain atypically.[102] Analyses of hepatic and splenic tissue for fat reveal no increase.[49,105,109] The material does stain with periodic acid-Schiff's reagent (PAS), may stain with Best's carmine and displays striking metachromasia.[113] Formalin or alcohol-fixed material dissolves the vacuolar material. Dioxane-dinitrophenol fixative has been useful[72] in preserving the deposited material.

Histochemical studies led Lindsay and his collaborators[72] to suspect that the storage material is glycoprotein. Brante[11] isolated a material, polysaccharide in nature, having 0.9 per cent sulfur, 27 per cent hexosamine, and 26 per cent glucuronic acid, containing no fatty acids by hydrolysis, and representing 10 per cent of the dry weight of the liver. Uzman[113] has recently described two storage materials isolated from the liver and spleen of these patients: (1) a complex polysaccharide containing glucose, galactose, hexosamines, and sulfate, soluble in water and formaldehyde but insoluble in other organic solvents, and staining metachromatically with toluidine blue; (2) a glycolipid soluble in water and ethanol but not in other organic solvents, and containing fatty acids, sphingosine, neuraminic acid, hexuronic acid, hexosamines, glucose, and galactose. These Uzman refers to as Fractions P and S, respectively.

Dawson[27] thought that the deposits in the brain consisted of phospholipid although those elsewhere seemed to be mucopolysaccharide. Uzman[113] did not study brain.

THE FUNDAMENTAL DEFECT

Straus, Merliss, and Reiser[105] thought that this might be a dystrophy of collagen, and Cole and his co-workers[19] also subscribed to this view. These authors based their view mainly on the lack of good evidence of this being a lipid-storage disease and the fact that contractures of joints and hernia occur, as well as skin changes which Cole interpreted as involving primarily collagen.

On the other hand, Ellis and colleagues[34] considered gargoylism (as they called it) a disorder of lipid metabolism. Washington[117] in his term "lipochondrodystrophy" implied the same theory.

de Lange and co-workers[29] and Strauss[106] thought the storage material might be a glycogen. Lindsay and co-workers[72] suggested that the stored material might be a polysaccharide (such as glycogen) or glycoprotein. Brante[11] studied three cases clinically and histologically and came to the conclusion that the Hurler syndrome is a "congenital enzyme disturbance as regards the metabolism of the mucopolysaccharide or of some of its components, or as regards the binding of the mucopolysaccharide to protein, etc." The qualitatively and/or quantitatively abnormal mucopolysaccharide accumulates at various sites, according to the last view.

Uzman[113] appears to take a slightly different view, which, however, to the nonchemist is not too evidently distinct. He holds that the genetic defect is one concerning the metabolism (i.e., synthesis) of "structural polysaccharides" which are normally important building blocks of connective tissue elements.[41]

The manner in which abnormal deposits occur in the intima and elsewhere is reminiscent of the handling in rabbits of methylcellulose and pectin,[53,54] both of which are macromolecular carbohydrates. Hueper[54] observed ballooning of cells in the liver, spleen, kidney, arterial intima, bone marrow, and anterior pituitary when pectin was administered intravenously in rabbits and dogs. However, "no lesion was found in the cerebral parenchyma, the vascular system of the brain or the choroid plexus."

The clinicopathologic differences between the Hurler syndrome, on the one hand, and the syndromes of Gaucher and of Niemann and Pick, on the other, are suggestive evidence that the storage material in the Hurler syndrome is not lipoid. In neither Gaucher's disease nor Niemann-Pick's disease are the parenchymal cells of epithelial organs involved. (Thannhauser[109] refers to Gaucher's disease as "reticular and histiocytic cerebrosidosis" and to Niemann-Pick's disease as "reticular and histiocytic sphingomyelinosis.") The bone lesions of Gaucher's disease, such as the Erlenmeyer flask deformity of the long bones, result from the involvement of the marrow and not from the implication of fundamental skeletal building blocks as in the Hurler syndrome.

The duality of the storage material, as demonstrated by Uzman,[113] requires explanation. He proposes that the accumulation of one may be a direct result of the genetic defect and the other an ancillary effect resulting from interference with normal cellular function as a result of the deposition of the first. Uzman[113] considers his Fraction P to be more directly concerned with the basic defect of this disease.

The fact that the skeletal deformity is invariable, whereas the mental retardation, corneal clouding, and hepatosplenomegaly are inconstant and progressive is consonant with the idea that the skeleton is affected in a primary manner by the connective tissue defect, and that the other manifestations are, in the main, secondary "storage" phenomena, a thesaurosis.

Meyer[78,79] states that chondroitin sulfate A, the main mucopolysaccharide of hyaline cartilage, has been identified in only one other tissue—cornea. There is a possibility, then, that the corneal involvement might be a primary feature of the syndrome, as we are presuming the dysostosis to be, and not a secondary feature due to deposit of an anomalous polysaccharide.

It is probable that the basic defect in the two genotypes of the Hurler syndrome (*v. seq.*) is slightly different. The phenotypic differences would suggest this to be the case.

INCIDENCE AND INHERITANCE

This disorder is more common in males than females. Few, if any, cases have been described in Negroes. The syndrome has been reported in Chinese.[87]

More often than not, the Hurler syndrome displays features of inheritance consistent with a recessive autosomal trait.[44] Parental consanguinity[8,44] is frequent, and affection of multiple sibs without the occurrence of affected individuals in the preceding generation ("familial" characteristics) is often the case. In the series of patients seen in this hospital, there is one instance of the disease in two sisters with normal parents and three normal siblings. There are no

well-documented descriptions of skeletal deformities in close relatives of patients with full-blown cases to suggest that partial expression of the trait in the heterozygous state may occur. Concordance in identical twin sisters has been described.[86] Craig[22] described the disorder in a twin brother and sister.

In 1952, Jervis[63] reviewed the information on 103 families described in the literature. When the ratio of affected to unaffected sibs was corrected by the method of Bernstein and that of Lenz, statistically significant agreement with the expected 1:3 ratio was obtained. Cousin marriages are *known* to have occurred in 11 of the 103 families and probably actually occurred in more. Using Hogben's formula, Jervis calculated that a 10 per cent consanguinity rate would correspond to a gene frequency of 1 in 40,000.

As far as is known, none of these patients has procreated. Some of the patients with milder affection may be capable of reproduction. Because of the statistical unlikelihood of mating with a carrier for the disease trait, unless the mate is a relative, the offspring of an affected person can be expected to be normal but will of necessity be a carrier for the trait if the theory of the recessive inheritance of the Hurler syndrome is correct. Actually the individuals most capable of reproducing are all males who may have the sex-linked variety of the disease (*v. seq.*). This means that none of their sons would be affected but half the daughters would be carriers.

A seemingly sex-linked form is described in at least five reports,[4,74,81,85,120] and, of course, there are many other instances in which this theory of inheritance is consonant with the known facts.[19,30,36,55,64,74,75] In these cases the inheritance follows the pattern of a recessive x-chromosome factor, such as hemophilia. Njå[85] suggested that cases without corneal opacity are most likely to show this mode of inheritance.

In the fascinating report by Beebe and Formel,[4] nine cases were described occurring in four generations of a family of Dutch extraction which has resided in the Catskill Mountains for about 250 years. Of 19 males, 9 were affected. Of 16 female siblings of affected males, none was affected. All 9 affected males were related through their mothers, who were presumably carriers. Furthermore, they were all descended from a common female ancestor who was almost certainly likewise a carrier or perhaps started the disease (by mutation), just as Queen Victoria probably initiated hemophilia[103] in the royal houses of Europe. Five other females could be identified as carriers by reason of affected brothers and sons. Six females had borne only normal children.

The family described by Beebe and Formel[4] may corroborate Njå's[85] impression that the sex-linked disease is a different entity clinically as well as genotypically. The sex-linked form of the disease may pass unrecognized until the age of 4 to 8 years. Mentation is usually less severely affected. The patients live longer. Finally, there is no corneal involvement. Fig. 3 presents the case of a patient with Hurler's syndrome, probably of the sex-linked variety.

After reviewing the literature on the Hurler syndrome in the light of the thought-provoking papers of Beebe and Formel[4] and of others, I have become convinced that there are at least two genotypes of the Hurler syndrome. Futhermore, it seems that there may be slight phenotypic differences corresponding to the genotypic differences, as outlined in Table I.

TABLE I

	AUTOSOMAL RECESSIVE	SEX-LINKED RECESSIVE
Corneal clouding	4+	±
Retardation of intellect	2+ to 4+	± to 2+
Gibbus	2+ to 4+	±
Age of death	Usually under 20 years	Often over 40 years
Reported cases	The majority, e.g., refs. 22, 47, 48, 63, 86, 93	Quite definite examples: refs. 4, 74, 81, 85, 120; likely examples: refs. 19, 30, 36, 55, 64, 74, 75
Personal cases	Probably fourteen cases	Probably two pedigrees (see Fig. 3 for one)

It would seem significant that most of the patients known to have survived beyond the age of 20 years (see above) were male. In Jervis' survey[63] there were 145 cases in which the sex was stated; of these, 93 (64 per cent) were male. Of 112 sibships, 65 could, by reason of the fact that all affected individuals were male, represent the hypothesized sex-linked variety of the disease. There were 27 sibships with more than one affected individual; of these, twelve had only males affected, only four had only females affected, and in eleven both males and females were affected. The average age of the affected individuals in the sibships with more than one affected individual, all males, was 6.65 years. The comparable value for the sibships containing both male and female affected individuals was 10.02 years. Although this appears to contradict the rough impression that the patients with the sex-linked variety of the Hurler syndrome are older when they come to medical attention and when they die, it must be remembered that these collected sibships may contain some in which the trait was inherited as an autosomal recessive; these may weigh down the average.

Again following Jervis'[63] survey the state of the cornea was analyzed in (1) the isolated female cases plus the sibships with affected persons of mixed sex, and in (2) the isolated male cases plus the sibships with affected persons all male. In the case of multiple affected sibs all affected persons in that sibship were counted as having cloudy cornea if one was said to show it. In sibships of the first type, the cornea was described in 69 individuals, of whom 51 (74 per cent) had corneal clouding. In category 2, the cornea was described in 70 individuals, of whom 39 (55.6 per cent) had corneal clouding.

Parents have been invariably unaffected. The difficulties in distinguishing autosomal from sex-linked recessive inheritance are well illustrated.

One may conclude that there are sex-linked and autosomal recessive forms of this disease, the latter being several times more common than the former.* If it were not for the confusion it would create, one might, with historic justification, refer to the disorder inherited as an autosomal recessive as the Hurler syndrome, and to that inherited as a sex-linked recessive as the Hunter syndrome (see Historical Note).

*In one report,[18] dominant inheritance is claimed, however.

DIFFERENTIAL DIAGNOSIS

At least superficially, there are many resemblances between the *Hurler syndrome* and the *Brailsford-Morquio syndrome.*[10,82] In fact, it has been claimed that the two syndromes occurred in different members of the same family.[8] Fig. 4 describes an experience which makes me skeptical of such reports. de Rudder[92] has suggested that the Hurler syndrome is merely a combination (through gene linkage) of Morquio's dysostosis with what he calls a "phosphatide diathesis." Actually, as was discussed in Section I, gene linkage probably plays no role in hereditary syndromes. Cases are pointed to in which it appeared that only the "phosphatide diathesis" existed, e.g., by Grebe.[43]

Brailsford-Morquio chondro-osteodystrophy was independently described about 1929 by the two observers[10,82] whose names identify the syndrome. Morquio's name is more commonly associated with the disease than is Brailsford's. The disorder[3,4,9,13,21,23,32,33,35,77,84,89,100,107,118,123] is usually first detected at the age of less than 1 year, when a thoracolumbar kyphos is noted. The disease is characterized by kyphosis and failure of the trunk to grow in length whereas the extremities grow in a more nearly normal manner. The patients are dwarfed. Radiologically the vertebrae display wedge deformities or, more commonly, platyspondyly, i.e., flat vertebrae. In the extremities there may be palpable enlargement of the epiphyses which may superficially suggest rickets, a frequent misdiagnosis. The skull, mentality, corneas, liver, and spleen are usually normal. These normal features and the relatively mininal affection of the limbs permit differentiation from the Hurler syndrome. In some cases the joints are hypermobile (as described by Morquio), but in others they exhibit limitation of motion. The evidence of an hereditary basis is clear-cut although the precise mode of inheritance is seemingly variable. The variable inheritance may indicate that a phenotypic similarity leads to classification together of several disorders which are fundamentally distinct. In Jacobsen's very interesting family[60] the disorder was traced through five generations with twenty affected individuals, all male. The genetic behavior was thought to be that of a sex-linked recessive like hemophilia. (Interestingly, two female carriers of the trait had "marked arthritic processes in the hips and ankles.") In other instances inheritance as an autosomal dominant or an autosomal recessive has been hypothesized.

The difficulties in differentiating the Morquio and the Hurler syndromes are illustrated by the siblings shown in Fig. 4. Although the disease in this brother and sister was labeled Morquio's syndrome earlier, hernia, contractures, deafness, "shoe-shaped" sella turcica, sagittal ridge of the skull (scaphocephaly), the marked affection of the extremities, and in one hepatosplenomegaly suggest the Hurler syndrome. It is true that neither of these patients has the marked deformity of the facial bones with noisy breathing as in the case of the Hurler syndrome. Furthermore, corneal clouding and mental impairment are not present. Here the syndrome seems to have been inherited as an autosomal recessive.

The difficulties of differentiating Morquio's syndrome and Hurler's syndrome are also well illustrated by the report of Davis and Currier.[26] Although entitled

"Morquio's Disease; Report of Two Cases," the patients were described as having striking hepatosplenomegaly, "shoe-shaped" sella, claw hands, and contractures in other joints. Most subsequent authors have accepted these as cases of the Hurler syndrome. Ruggles[93] applied the label of Morquio's syndrome to the disorder present in three members of a sibship totaling seven. However, the presence of deafness, mental defect, and cloudy cornea makes the Hurler syndrome likely.

As in the "collagen-vascular" group of acquired connective tissue diseases, there appears to be in the group of chondrodystrophies a clinical spectrum such that one entity blends smoothly into the next and it becomes impossible to say with certainty where one entity leaves off and the next begins. With the "collagen-vascular" group, increasing familiarity has sharpened up the boundaries of the individual entities. It is to be hoped that the nosography of chondrodystrophies will be advanced to a like degree. It is my impression that there are several entirely distinct dysostoses such as Morquio's and Hurler's, and that it is only our ignorance which results in confusion of one with another. Quite the opposite view, namely, that Morquio's syndrome and Hurler's syndrome are clinical variants of what is fundamentally the same disorder, is expressed by Eichenberger.[31]

Reduced joint mobility such as is seen in the Hurler syndrome is a characteristic of *arthrogryposis multiplex congenita*. In fact, in an extensive recent survey James[60] prefers to use the designation of "multiple congenital articular rigidities" as suggested by Nové-Josserand, rather than the more generally used term proposed by Stern.[104] Subluxation, especially of the hips, may occur in this condition of tight joints just as it does with the loose-jointedness of the Ehlers-Danlos syndrome. Rigidity of the temporomandibular joint may create a feeding problem in severely affected infants. The patella may be rudimentary or absent. The subcutaneous tissues are likely to feel thick, doughy, and gelatinous. In general the subcutaneous tissues may be deficient, or may be excessive so that the limbs have the appearance of stuffed sausages. The peripheral circulation tends to be poor and the limbs cold. Inguinal hernia occurs as well as congenital anomalies such as hypospadias, cleft palate, cryptorchidism, micrognathia, and mental deficiency. Usually othopedists are consulted for the joint manifestations. The ages of reported cases vary from prematurity to the age of 61 years.

From the above brief survey it is evident that there are many features of arthrogryposis, such as the changes in the articular structures and skin and the occurrence of hernia, all from a very early age, which suggest an *heritable* disorder of connective tissue. However, up to 1951 James[60] could find not a single instance of more than one case in the same family. There had been several reports of the disorder in one of twins who appeared to be uniovular.[50,73] These interesting observations cast doubt on both of the two leading theories for the etiology of this condition: (1) an adverse influence of the intrauterine environment; (2) heredity.

Also, to be differentiated from the Hurler syndrome are cleidocranial dysostosis, craniofacial dysostosis of the Crouzon type, Leri's familial plenosteosis[70,114] (to be described in Section VIII), acrocephaly.[88]

The Hurler syndrome was thought to be associated with xanthomatosis and called familial dermo-chondro-corneal dystrophy by François.[40] Rare xanthoma-like lesions were found in the skin in one of my cases (F. M. O'N., Rosewood 4821). Tay-Sachs' disease and the Hurler syndrome bear certain superficial resemblances to each other, and a presumed intermediate form is described by Jervis.[62]

Clinically, cretinism is another frequent misdiagnosis and is often the basis for referral of these cases to endocrinologists. However, the patient with the Hurler syndrome is usually active in his movements and displays normal cutaneous circulation. Tests of thyroid function are usually normal. Bone age is little delayed in the Hurler syndrome and the epiphyseal changes characteristic of cretinism do not occur. Secondary hypothyroidism from involvement of endocrine glands is theoretically possible.

The histologic changes in the brain resemble those of Tay-Sachs' juvenile amaurotic idiocy.[110] The rest of the picture permits differentiation, of course.

Inclusions in the leukocytes said to be indistinguishable from those described in the Hurler syndrome occur as an isolated hereditary trait, the Adler anomaly.[65]

OTHER CONSIDERATIONS

As with the other multifaceted syndromes studied in this series, diverse specialists such as surgeons (*in re:* hernia), otolaryngologists (*in re:* deafness, rhinitis), ophthalmologists (*in re:* corneal abnormality), psychiatrists (*in re:* mental deficiency), cardiologists (*in re:* cardiac abnormalities), orthopedists (*in re:* skeletal deformity) endocrinologists (*in re:* differentiation from cretinism) see these patients for the individual complaints which comprise the total picture.

The nosography of the Hurler syndrome has already begun to follow the pattern of so many other hereditary syndromes: it is at first considered to be largely a pediatric disorder simply because only the most severely affected individuals are identified. These individuals are so severely affected that they are unlikely to survive to adulthood and come to the attention of the internist. Because of the wide variability in expressivity which the student of hereditary disease comes to expect, the occurrence of mildly affected individuals in the adult age group is not surprising. It is entirely reasonable to believe that procreation by these individuals is possible. A 19-year-old patient of Ashby, Stewart, and Watkins was sexually mature.[2] (The authors stated: "Sexual development exceeds the normal.") Mental capacity may be little restricted: one of the patients of Barr and co-workers was an agricultural engineer. Ullrich[112] was one of the first to write in detail about the "late form" of the disease as he called it in contradistinction to the "infantile form." (These are undesirable terms since they may lead to the same confusion which has existed in the case of osteogenesis imperfecta.) He considered it likely that the 47- and 40-year-old patients described by Schmidt in 1938[97] as suffering from "a previously undescribed form of familial degeneration of the cornea in association with osteoarthropathy" and earlier (1927) by Schinz and Furtwängler[95] as "hereditary osteoarthropathy with recessive inheritance," suffered from a mild ("late") form of the Hurler syndrome. Of 11 children of consanguineous parents (first cousins), two daughters had died

at the age of 8 and 18 years, respectively. They showed markedly crippling stiffening of their joints. Scharf[94] described a 28-year-old man, Grebe[43] described patients 21, 24, and 30 years old, Hooper[51] had patients aged 20, 30, and 37 years, and Barr and co-workers[102] had patients 28 and 29 years old. Schwarz and Gagne[98] had a 37-year-old patient who was still living. Zierl[124] reported on a 21-year-old man and Noller[84] on a 43-year-old woman. Cocchi[16] provides two photographs of a patient, one taken when he was 4 years old, the other when he was 22. Cole and associates[19] had a 23-year-old patient.

Hurler[56] stated that mydriasis was unusually marked and prolonged after homatropine but sweating from pilocarpine less than normal.

No definitive treatment for the Hurler syndrome is known. Hurler,[56] in one of her original cases,[58] observed that thyroid extract, while having no measurable effect, produced subjective improvement in the patient. We have observed the same phenomenon (Fig. 3).

SUMMARY

In the Hurler syndrome, the characteristic features are skeletal deformity, limitation of joint motion, hernia, hepatosplenomegaly, cardiac abnormality, corneal opacification, deafness, and mental retardation.

The basic pathology is the distention of cells of many organs with material of two types: a complex polysaccharide and an aglycolipid. The fundamental defect may concern either the mucopolysaccharide or "structural polysaccharide" of connective tissue.

The Hurler syndrome is usually inherited as an autosomal recessive trait, less commonly as a sex-linked (x-linked) recessive. Clinical differences between the two genotypes appear to exist (see Table I).

Other chondrodystrophies, especially that of Brailsford and Morquio, display many features in common with the Hurler syndrome.

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